Combined modality adjuvant therapy for high-risk endometrial cancer

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The incidence of endometrial cancer has steadily increased over the past decade, with 320 000 new cases reported worldwide in 2012.[1] Endometrial cancer is the fifth most common cancer in women, and incidence is projected to increase[2] because of an increased prevalence of obesity and an ageing population. Although most patients present with early-stage low-risk disease, a rise in incidence is expected to lead to an increasing number of high-risk cases at presentation. This heterogenous group of tumours is characterised by higher grade and stage, deep myometrial invasion, lymph-vascular space invasion, or non-endometrioid histologies, such as serous or clear-cell cancers. Despite optimum surgical treatments, these tumours have an increased risk of local and distant recurrences and are therefore considered targets for adjuvant therapy. External beam radiotherapy showed a significant reduction in the risk of local relapse compared with observation, but did not show a significant survival advantage in a high-risk subgroup meta-analysis.[3]

Although endometrial cancers are generally radiosensitive and local relapse might be prevented by radiotherapy, many patients with high-risk disease still have distant metastatic relapses. Therefore, a systemic treatment with adjuvant chemotherapy was proposed as a solution, with or without radiotherapy. Randall and colleagues[4] previously randomly assigned 396 patients with stage III–IV endometrial carcinoma to adjuvant chemotherapy versus whole-abdominal irradiation and showed a survival benefit for adjuvant chemotherapy. Hogberg and colleagues[5] pooled the data of the NSGO-EC-9501[6] and the MaNGO ILIADE-III trials and reported on 534 patients randomly assigned to either radiotherapy or combined sequential radiotherapy and chemotherapy in the adjuvant setting. The NSGO-EC-9501 study and both studies combined showed a significant improvement in progression-free and cancer-specific survival in the combined treatment group.

In *The Lancet Oncology*, Stephanie de Boer and colleagues[7] report the first results of the multicentre PORTEC-3 randomised trial, focusing on toxicity and 2-year quality in those who received radiotherapy and those who received chemotherapy plus radiotherapy. Overall, 686 women were randomly assigned (330 to receive chemotherapy plus radiotherapy and 330 to receive radiotherapy alone). Baseline characteristics in both groups were well balanced, although comorbidity rates were higher in the combined therapy group. Toxicity and quality of life data were available for 660 patients and showed a higher incidence of severe adverse events and patient-reported symptoms in the combined group with radiotherapy and chemotherapy, mainly related to the well known side-effects of paclitaxel and carboplatin therapy. Most patients with adverse events recovered quickly after the end of the treatment, although peripheral sensory neuropathy was deemed troublesome by a quarter of all patients in the combined group at 2 years. Although the toxicities of combined treatment were shown to be manageable, whether this investment of adding chemotherapy will be rewarded by an improved outcome in the long term remains unclear. The fact that a toxicity and quality of life analysis were included as secondary endpoints in the trial design, which was not the case for the combined NSGO-EC-9501 and MaNGO ILIADE-III trials,[5] is a merit to the researchers. However, the trial had a few limitations. More than a third of all patients in both groups did not receive a complete staging surgery, including lymphadenectomy, because lymphadenectomy was optional. This could lead to the underestimation of stage IIIC disease in which the addition of chemotherapy has been shown to increase survival.[4,5] Although two large randomised trials[8,9] could not establish the value of a systematic lymphadenectomy in stage I endometrial cancer, the number of high-risk cases in these studies was rather small. To establish the value of a pelvic and para-aortic lymphadenectomy in high-risk endometrial cancer, the STATEC study (Selective Targeting of Adjuvant Therapy for Endometrial Cancer, NCT02566811) is in preparation at present. Furthermore, if future results of the PORTEC-3 trial confirm the progression-free and cancer-specific survival benefit for the combined treatment group observed in the combined NSGO-EC-9501 and MaNGO ILIADE-III trials, the

question remains of how much radiotherapy adds to the observed effect of adjuvant chemotherapy. This will be addressed by the results of the ongoing GOG-258 trial (NCT00942357), studying the same combined chemoradiotherapy regimen as in PORTEC-3.

Overall, the study by de Boer and colleagues clearly shows the feasibility of combined modality therapy for high-risk endometrial cancer. If the study shows a survival benefit for the adjuvant chemotherapy plus radiotherapy, combined therapy is expected to become the standard-of-care for high-risk endometrial cancer. With the present data on toxicity and quality of life, the (yet to be determined) survival benefits of chemotherapy can be weighed against the adverse events and quality of life measures reported in this study, which will improve the adjuvant therapy for women with high-risk endometrial cancer.

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We declare no competing interests.

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